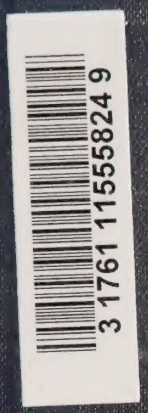

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INTRODUCTION

1.1 The Medical Research Council (MRC) has approved guidelines which its grantees must follow in the performance of research involving recombinant DNA molecules. These guidelines classify experiments by degree of risk and require use of specified physical and biological safety procedures proportionate to these risks. Other government departments (NRC, NHW and Agriculture) have adopted the same rules for research under their own jurisdictions; however, the guidelines do not apply, except on a voluntary basis, to recombinant DNA research in private foundations, in industry, or under provincial jurisdiction.

1.2 Potential benefits from recombinant DNA research seem to be considerable; however uncertainty continues to exist concerning the associated risks. This paper reviews these risk-benefit considerations, and discusses various options for the control regime to be applied to recombinant DNA research in Canada. It is being published at this time to indicate the factors which the government has considered in its deliberations on recombinant DNA and to provide information which may assist the public to participate in assessing the implications of this research.

BACKGROUND:

Recombinant DNA:

2.1 DNA, deoxyribonucleic acid, is a class of molecules which control the reproduction, growth, and function of all living cells. This paper is concerned with research techniques involving recombinant DNA, which is constructed by chemically isolating DNA fragments from the cells of one organism and combining these fragments with the DNA of a "vector" or carrier (often a virus). The vector is then used to insert the recombinant DNA into a "host", usually a bacterium, which in essence becomes a new type of organism, exhibiting as it reproduces the properties specified by both its own DNA and the inserted recombinant DNA.

Benefits and Risks:

2.2 The development of recombinant DNA techniques in 1973 has caused considerable excitement within the scientific community. The construction and reproduction of recombinant DNA molecules promise breakthroughs in basic genetic science by allowing much more rapid and precise identification, isolation, concentration and manipulation of genes (a gene is a DNA fragment which controls one or more specific cell functions) than was hitherto possible. The techniques are already being used to study antibiotic resistance in bacteria. Other predicted advances include the further understanding of cancer mechanisms, clarification of the processes by which the human body develops immunity to disease, and more effective treatment of genetic diseases such as hemophilia and sickle cell anemia.

2.3 Recombinant DNA techniques may also have industrial and other practical applications. For example, the recent use of recombinant DNA techniques to insert into bacterial hosts the genes responsible for insulin production in rats suggests that bacteria may eventually be developed as a source of insulin for human medical purposes. In theory, similar approaches could eventually be used to engineer bacteria which could produce antibiotics, hormones, vitamins, and other medically and industrially important chemicals; bacteria which could "eat" oilspills or selectively concentrate precious metals in sea water; algae which could usefully liberate hydrogen from water for energy production purposes; and plants, notably grains, which could fix nitrogen from the air instead of requiring fertilizer.

2.4 The prospects for benefits must, however, be weighed against the potential hazards which are inherent in the nature of the research. Fears have been expressed by some scientists that microorganisms may be genetically altered by recombinant DNA manipulation, either as an unexpected laboratory result or through accidental or improper laboratory procedures, so as to become hazardous to human health or the environment. The fact that these research products would be new organisms capable of reproduction and multiplication has been cited as a radically different property which is not encountered with other dangerous laboratory substances. Moreover, the escape from a laboratory of such organisms might not even be recognized until the organisms established themselves as viable species, and even then there would be no guarantee that the organisms would be retrievable or destroyable. The risks of these prospects are magnified, critics argue, because most recombinant DNA research uses certain strains of E. coli bacteria as the host organism. E. coli occurs naturally in the digestive tracts of all animals, including humans (and therefore in sewage systems, waterways and elsewhere), a fact which some believe could possibly turn inadvertent recombinant DNA results into a widespread health hazard.

2.5 Examples of hazards which some scientists believe could arise through recombinant DNA experimentation include: E. coli capable of causing cancer or synthesizing botulinus, diphtheria or other toxins; disease-producing bacteria unnaturally resistant to antibiotics; virulent strains of bacteria which are currently harmless. There have also been warnings that beneficial applications of recombinant DNA research could have unfortunate consequences. For example, bacteria designed as an oilspill counter-measure might colonize oil wells or pipelines, and the escape of insulin-producing bacteria from an industrial laboratory or production facility might conceivably cause insulin poisoning in sections of the population.

2.6 A few scientists have also argued, although in the face of considerable criticism from many of their colleagues, that new organisms produced through recombinant DNA techniques may pose fundamental

and far-reaching ecological risks. The combination in one organism of genes from two totally different species, or indeed two different types of organism (e.g. bacteria and animals), has been cited as a crossing of boundaries which, through the evolutionary process, have been established as naturally inviolate. This creation of "artificial" organisms which could probably never come about in nature could, according to this view, disturb the entire ecological balance, and have profound disruptive effects on many life forms, possibly inlcuding man.

2.7 At this stage, recombinant DNA research is marked by its uncertainty. These techniques are relatively new; the research which they permit literally defines the frontiers and rate of development of advancing genetic and microbiological knowledge. It is therefore impossible to predict when various beneficial applications could come to fruition or to accurately determine probabilities of the high risk scenarios, although there are recent indications that these probabilities may be lower than critics originally suggested. However, regardless of how low these probabilities may be, it has been feared that the risks could accrue not just in the application of research results, but in the actual conduct of the research itself. The resulting potential for hazard is magnified by the relatively embryonic state of scientific knowledge concerning various genetic processes, which suggests that factors currently unknown and therefore impossible to anticipate could emerge as unexpected and hazardous consequences of even the most carefully performed experiments.

Guideline Formulation:

2.8 Concern about the risks of certain types of recombinant DNA experimentation led to a call in 1974 from several leading scientists, through a committee of the United States National Academy of Sciences, for a world-wide moratorium on these experiments. In February, 1975, an international scientific conference at Asilomar, California, recommended that recombinant DNA experimentation could proceed, provided adequate safeguards were in place. Subsequently, guidelines to govern recombinant DNA experimentation have been formulated by the National Institutes of Health (NIH) in the United States and by the Department of Education and Science in Great Britain. Several other countries (including West Germany, Switzerland, Sweden, Denmark, Holland, Israël, the Soviet Union, Australia and New Zealand) have prepared, or are preparing, guidelines based on those of the United States or Great Britain (and in some cases both) for recombinant DNA research within their borders. In addition, organizations such as the European Molecular Biology Organization, the International Council of Scientific Unions, and the World Health Organization are reviewing international aspects of recombinant DNA research.

2.9 Following the Asilomar conference, the Medical Research Council (MRC) took the lead in reviewing

recombinant DNA research in the Canadian context. A committee, chaired by Dr. L. Siminovitch of the University of Toronto, submitted to MRC in June, 1976, a draft report proposing guidelines which MRC grantees should follow in research involving recombinant DNA molecules, and certain hazardous animal viruses and cells. These guidelines were substantially modified in light of comments received from other government departments and granting agencies, universities, scientific societies, and industry (specifically the Pharmaceutical Manufacturers' Association of Canada), and were formally approved by the Medical Research Council on February 22, 1977.

2.10 The MRC guidelines for recombinant DNA research are similar in most respects to those adopted by the NIH, and subsequently by other government departments and agencies, in the United States. They forbid experimental work by MRC grantees which would deliberately create recombinant DNA expected to result in harmful products, deliberately release organisms containing recombinant DNA into the natural environment, or transfer drug resistance to microorganisms not known to acquire it naturally if such acquisition could compromise the effective use of the drug. The guidelines allow other recombinant DNA experiments, but classify them according to the degree of risk involved (with the exception of certain experiments which would be assessed as individual cases by MRC), and specify combinations of physical and biological containment procedures and facilities which must be used to minimize these risks.

2.11 Physical containment refers to techniques and equipment used to physically prevent microorganisms from infecting laboratory staff or escaping from the laboratory. The guidelines identify six levels of physical containment, specifying laboratory design features and operating procedures proportionate to the hazards to be contained. The least stringent, level A, requires no special design features beyond those suitable for a well designed and operated microbiological laboratory; the most stringent, level F, requires design and operating procedures similar to those of maximum security biological warfare establishments.

2.12 The guidelines also specify four levels of biological containment for use in recombinant DNA research with host-vector systems involving *E. coli* bacteria (currently the only host-vector systems widely utilized). The lowest level of biological containment requires the use of unmodified *E. coli* K12, a special laboratory strain of the bacteria generally believed to be incapable of colonizing the normal human bowel. The other levels of biological containment require use of EK12 host-vector systems genetically disabled so as to reduce, to an increasing degree as higher containment is desired, their ability to survive outside the special laboratory conditions.

2.13 In addition to dealing with recombinant DNA, the MRC guidelines also specify physical containment procedures to be used in research involving hazardous animal viruses and cells. This makes the MRC

guidelines somewhat more comprehensive than those adopted in other countries. However, in light of the uniquely different nature of recombinant DNA research and in recognition of the unprecedented problems it may pose, this paper is concerned with only those aspects of the guidelines which are relevant to recombinant DNA.

2.14 Implementation of the guidelines, which has already begun, will involve three levels of responsibility. At the laboratory level, the principal investigator will be responsible for ensuring that adequate facilities are available and that proper procedures are followed. The institution, through a "biohazards committee", will be responsible for monitoring facilities and procedures on a continuous basis, and for advising MRC on whether the guidelines are being followed. MRC will be responsible, through its control of research funds, for ensuring that the guidelines are being followed. Moreover, MRC, recognizing both the present uncertainty and the rapid advances that are possible with respect to recombinant DNA, has adopted a flexible approach to the guidelines, and will be responsible for continually reviewing and, as necessary, revising them.

2.15 The National Research Council has adopted the MRC guidelines for research carried out both within its own laboratories and also by its grantees. In addition, the Departments of Agriculture and National Health and Welfare have announced that any recombinant DNA research under their jurisdictions would also be done in compliance with the MRC guidelines. Outside the federal government, the National Cancer Institute of Canada and the Conseil de Recherche en Santé de Québec have also adopted the guidelines.

Public Debate on Recombinant DNA Research:

2.16 The proposal of a moratorium on certain recombinant DNA experiments was the beginning of a heated controversy within the scientific community. Since that time, reputable scientists have outspokenly advocated widely varying opinions, ranging from demands for a total ban on recombinant DNA research to claims that there is little danger involved. The unusual vigour with which these and other arguments have been pressed has led to an unprecedented degree of rancour within the scientific community, especially in the United States. Inevitably, these discussions have spilled over into the public arena, as critics claim that control of research which could potentially pose serious risks to society should not be left in the hands of scientists.

2.17 To date, the most prominent example of public participation in this debate in the United States has occurred in Cambridge, Mass. As a result of concerns expressed by the city's Mayor, Harvard University's plans to construct high level containment facilities for recombinant DNA research were reviewed by a committee of lay people appointed by the City Council. The decision of this committee, after considerable

debate, was accepted, namely that recombinant DNA research could proceed in Harvard under controls slightly more stringent than those required by the NIH. In addition, there will be a continuing, independent review by a citizens' group.

2.18 Continuing media coverage of the Cambridge incident and other aspects of the recombinant DNA debate has prompted politicians and regulatory bodies to legislative action in various jurisdictions throughout the United States. At the municipal level, Cambridge, Princeton, Bloomington and San Diego have had public discussion about recombinant DNA regulation, and legislation has been considered, though not finalized, at the State level in New York, California and New Jersey. In addition, several bills proposing controls over recombinant DNA research have been, or are being, debated in both chambers of the United States Congress.

2.19 In general, the proposed U.S. Federal bills seek to ensure that safety provisions cover, by force of law, recombinant DNA research in all sectors including industry. The NIH guidelines (which have recently been modified to reflect latest scientific findings that certain risks are less serious than was originally believed) are taken as the initial basis for these safeguards. A flexible approach would be adopted and any regulations would be subject to continuing review and change by a responsible regulatory agency. Licensing of laboratories to perform recombinant DNA research is envisaged, as is monitoring and enforcement on the part of a regulatory agency. The different bills have been at variance with respect to: the nature of the regulatory agency to be involved, whether or not national regulations should supersede local safety provisions, the extent to which proprietory information can be protected from public disclosure and the penalties to be imposed on violators. These points have been the subject of intensive Congressional discussion and vigourous lobbying by the scientific community in recent months, and the form and timing of Federal recombinant DNA legislation is still uncertain.

2.20 The eventual adoption of a legislative approach by the United States would almost certainly result in pressures for similar action in other countries. To date, Great Britain is the only other nation which has tied safeguards for recombinant DNA research to a legal framework; by August, 1978, all such experimentation will be subject, under conditions of prior notification, to the Health and Safety at Work Act.

Recombinant DNA Research in Canada:

2.21 To date, there has been little recombinant DNA research in Canada. As far as is known, no experimentation was carried out in government laboratories or under government funding prior to preparation of the MRC guidelines, although portions of certain experiments were carried out in the United States under the NIH guidelines.

2.22 Now that the MRC guidelines have been adopted, a limited amount of recombinant DNA research is getting under way. MRC is receiving applications for support of various experiments under the guidelines, and anticipates supporting 10 to 15 university research projects in the coming year. NRC has also indicated that it will be funding recombinant DNA research by two of its grantees. Two programs which may involve recombinant DNA experimentation in NRC laboratories are also under consideration, and biohazard committees have been established to review these projects. Representatives from the Departments of National Health and Welfare, Agriculture, Fisheries and the Environment, and National Defence have indicated that their departments presently have no plans to conduct or fund recombinant DNA research.

2.23 Outside the funding aegis of the federal government, the National Cancer Institute, which has adopted the MRC guidelines, is also providing support to some of the recombinant DNA research projects being funded by the federal granting agencies.

2.24 The situation with regard to industrial recombinant DNA research is uncertain. It is unknown at this time whether any such research is going on in Canada, although there are several pharmaceutical laboratories in this country which would be capable of carrying out research along these lines. Many of these belong to Canadian subsidiaries of American firms which <u>are</u> conducting recombinant DNA research, and which have not been totally consistent as to whether or not they will implement the NIH guidelines.

<u>FACTORS</u>:

<u>Scientific Considerations</u>:

3.1 From the point of view of danger to the environment and to public health, research with recombinant DNA is characterized by the uniqueness of its potential hazards and by the uncertainty as to whether these hazards could arise. Scientific opinion is divided. Eminent scientists argue that the research poses no significant dangers; others point out that the potential hazards, even if statistically improbable, are so potentially momentous that all research in the area should be stopped; some see no problems with recombinant DNA at the "basic research" level, but fear misguided or inadvertent applications of research results; many, probably the majority of scientists, feel that recombinant DNA research should proceed, providing adequate safeguards are observed.

3.2 There is little doubt that recombinant DNA techniques constitute an elegant experimental approach which could allow rapid advances in basic genetic science. As for potential applications, proponents of the research argue that the benefits which could accrue to society justify the risks involved. Critics point out, however, that it is still uncertain whether these applications will come to fruition, and that, in any case, they are not nearly as immediate as the suggested risks.

It is further argued that alternate techniques, though admittedly much more time-consuming and painstaking, can allow advances in many of the scientific areas concerned, and thereby constitute less risky and more acceptable approaches to many of the potential applications. These claims are not completely convincing, however, and it does appear that recombinant DNA techniques do offer certain unique possibilities which cannot be matched by other laboratory methods.

Regulatory Considerations:

3.3 The dominant view within the scientific community is that recombinant DNA research should proceed, provided that precautions like those required in the MRC guidelines are taken to minimize the risks. It is also generally agreed, however, that such precautions must apply in all sectors, and it is in this respect that the guideline approach provides incomplete coverage. It is fully expected, for example, that MRC can ensure compliance of its grantees with its guidelines, and that other recombinant DNA research conducted under federal financial auspices can be similarly regulated. The guidelines do not, however, apply to research funded by other sectors, and compliance by laboratories of provincial governments, private foundations and industry would be of a voluntary nature at best.

3.4 Many of the potential recombinant DNA applications could be of significant commercial value. The Department of Industry, Trade and Commerce is aware of this, and will continue to assess whatever possibilities may arise for achieving Canadian industrial benefits through selective encouragement of this research. In any case, industrial proprietary preoccupations would ensure that recombinant DNA studies would be conducted in secrecy, thus making it extremely difficult under a "guidelines only" regime to be certain what experiments are being carried on in industry and what safety procedures are in effect.

3.5 Government legislation of a control regime for recombinant DNA research, like that proposed in the United States and Great Britain, could ensure complete sectoral coverage of whatever safety provisions are deemed desirable. One possibility here would be a total ban on the research, which could be claimed to be a firm step to protect public health and the environment. It might also be argued that a very strict, temporary control regime could allow Canada to wait until the uncertainties and risks associated with this research are reduced through experimental work elsewhere.

3.6 On the other hand, a ban or very strict regulation of recombinant DNA research would have disadvantages. Licensing and inspection procedures might prove costly and administratively complex. Access to the potential benefits of the research may be unnecessarily delayed. It would be argued, as it already has been with respect even to voluntary guidelines, that external controls constitute an unwarranted and unprecedented interference with the search for knowledge and the freedom of scien-

tific enquiry. Moreover, control measures whether in the form of guidelines or legislation, must be perceived to be reasonable if compliance is to be obtained. The technical and financial impediments to the conduct of recombinant DNA research are not very severe, and a control regime which is considered unreasonably restrictive could easily lead to clandestine research under inadequate containment procedures.

3.7 It must also be recognized that the rate of advancement of scientific knowledge with respect to recombinant DNA and genetic processes promises to be very rapid. Thus, a control regime that seems appropriate today will probably need to be changed as time passes and more experience is gained. The MRC guidelines, like those of other countries, have been designed in full recognition of this prospect; they will be subject to continuing review by MRC's biohazards committee and will be altered, on the recommendations of this committee, as scientific knowledge accumulates.

3.8 Various international considerations also impinge on Canada's choice of a control regime. On the one hand, a comparatively relaxed control regime in this country could encourage the shifting of more hazardous research projects to Canada, especially in the industrial sector. On the other hand, a control regime which is much more restrictive than the international norm would not necessarily be completely effective as a domestic public health and environmental safety precaution, since international borders are not likely to provide any defence against hazardous recombinant DNA - containing organisms originating abroad. Moreover, an unusually severe control regime would be questioned as to its scientific justification and could be viewed with disrespect on the part of researchers. Such an approach could also unduly restrict Canadian scientists in developing the knowledge and expertise which would allow them to evaluate the results of recombinant DNA research carried on abroad, and might possibly lead to the emigration of scientists to countries with more liberal regimes.

Public Involvement Considerations:

3.9 Consideration of legislative possibilities for control of recombinant DNA research reflects the growing view that this is a general public policy issue. In the United States heated public debate has focussed on the potential hazards and benefits, but also on the moral, ethical and social implications of the creation of new life forms and the very real possibilities which the techniques offer for the development of human gene therapy and the engineering of human genetic characteristics.

3.10 In Canada, press coverage of the guidelines and of the issue of recombinant DNA research has been fairly widespread, although there has been little analysis or editorial comment. Little public discussion seems to have been stimulated; while it might be expected that the organized expression of public concern in the United States would have

eventual echoes in this country, there is little indication of this at present.

3.11 There is a measure of public involvement in the existing recombinant DNA control regime in that the MRC biohazards committee charged with reviewing the guidelines has a "lay" Chairman and a majority of "lay" members. However, further public involvement would be valuable, from the point of view of assistance to the government in the formulation of the control regime, and also as a process of public education with respect to this complex matter.

ALTERNATIVES:

Control Regime:

4.1 In the Canadian context there are several alternatives as to the degree of control and supervision which might be exercised over the conduct of recombinant DNA research.

4.2 ALTERNATIVE I would be a continuation of the present situation, i.e., implementation of the MRC guidelines by MRC and other departments and agencies of the federal government, and voluntary compliance on an unregulated basis by other sectors, including industry.

4.3 This alternative is favored by the following points:

(a) No administrative machinery would be required beyond that already planned.

(b) Interference with the scientific community would be kept to a minimum.

(c) Flexibility with respect to evolution of the guidelines would be maximized.

4.4 Disadvantages of this alternative would be:

(a) Compliance by researchers funded other than by federal auspices, especially in industry, could not be guaranteed.

(b) Incompleteness of coverage could result in public health and ecological hazards.

(c) Canada's control regime would be less restrictive than that which is being or is likely to be adopted in other countries, with resultant possibilities of transfer of riskier recombinant DNA research activities to this country, especially in the industrial sector.

4.5 ALTERNATIVE II would involve the extension of the guidelines to cover, on a compulsory basis by law, recombinant DNA research in all sectors. Registration and licensing of all laboratories and facilities using or otherwide handling recombinant DNA molecules, or organisms arising therefrom, would be required. Patent and product licensing provisions could also be made subject to compliance with the guidelines.

4.6 One approach to this alternative would be to pass new legislation specifically to govern recombinant DNA research; however, the MRC guidelines could also be given the force of law, and procedures could be established for registration, licensing and inspection, by means of regulations under the National Health and Welfare Act. (This would not include patent and product licensing powers.) Enforcement of these provisions would rest with the Department of National Health and Welfare, although for administrative purposes NRC and MRC could continue monitoring their own grantees. Modifications of the guidelines on which the regulations were based could remain with MRC, although the final authority for the provisions of the regulations would rest with NHW.

4.7 Advantages of this alternative would include:

(a) Compliance with safety provisions would be required by law in all sectors.

(b) More complete coverage would provide greater protection to public health and the environment.

(c) Canada's control regime would be consistent with those being established in other countries.

4.8 Disadvantages of this alternative would include:

(a) The passage of new legislation to specifically govern recombinant DNA research would probably involve a time delay inappropriate to the needs of the present situation (however, establishment of regulations under the Health and Welfare Act could be accomplished quickly, by means of an Order in Council).

(b) Registration, licensing and inspection would require expansion of existing regulatory machinery, although this would probably be minimal.

(c) The scientific community might object to this degree of interference with the freedom of scientific enquiry.

4.9 ALTERNATIVE III would require, by force of law, that all recombinant DNA research, or all such research assessed to have a certain degree of risk, be carried on in a few centralized, highly secure facilities, possibly provided by the government.

4.10 Advantages of this approach are:

(a) There would be assurance that the most

hazardous experiments (or all experiments) would be carried out under standard supervised conditions designed for maximum safety.

(b) Risks to public health and safety would be lower than for alternatives I and II above.

(c) It would be relatively easy to control and oversee research carried out in the centralized facilities.

4.11 Arguments against this option include:

(a) The government would probably have to establish, and perhaps operate, the centralized facilities.

(b) New legislation would be required to authorize the licensing of selected laboratories while prohibiting recombinant DNA research elsewhere.

(c) Inspection to ensure compliance would be more demanding, particularly if the regime was considered unreasonably restrictive.

(d) Construction of the facilities and scheduling of access to them would probably delay many research projects.

(e) Elaborate procedures for protection of proprietary rights would have to be established if industrial research were to be carried out in the central facilities.

4.12 ALTERNATIVE IV would be a total moratorium on recombinant DNA research in Canada. This could probably be accomplished through moral suasion or government directive with respect to federally funded research; however, new legislation or perhaps regulations under the National Health and Welfare Act would be required to ensure extension of the moratorium to research not funded by the government.

4.13 The advantage of this approach would be:

Protection of public health and the environment would be maximized while, at least in the case of a temporary moratorium, still allowing Canada to eventually benefit from the research.

4.14 Disadvantages of this option are:

(a) Compliance with any moratorium other than that attempted through moral suasion would require extensive inspection and enforcement measures.

(b) Canada's control regime would be inconsistent with those adopted in most other countries.

(c) The scientific community would probably react very negatively, citing technical objections to a moratorium and unreasonable interference with scientific research.

(d) Perceptions that the moratorium was unreasonable could lead to significant non-compliance.

(e) Possible benefits from recombinant DNA research (including industrial benefits) would be delayed.

(f) Canadian scientists might not develop the knowledge required to evaluate results of recombinant DNA research carried on elsewhere, or to take protective measures in the event that hazardous recombinant DNA organisms cross Canadian borders.